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CASE 4-31824B/SKB

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II 20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
JOHN R. DALES
APPLICATION NO: 09/265,926
FILED: MARCH 11, 1999
FOR: PREPARATION OF PURINES

Art Unit: 1624
Examiner: M. Berch

Assistant Commissioner for Patents
Washington, D.C. 20231

APPELLANTS' BRIEF (37 CFR § 1.192)

Sir:

In compliance with the requirements of 37 CFR§1.192(c), Appellant hereby submits this brief in triplicate.

I. Real Party in Interest

Novartis International Pharma, Ltd. is the owner of the entire right, title and interest to the invention disclosed in the patent application by virtue of an assignment from the original assignee, SmithKline Beecham Corp., who in turn was assigned the invention by virtue of an assignment from the inventors.

II. Related Appeals and Interferences

With respect to other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in the appeal, there are no such appeals or interferences.

III. Status of Claims

Claims 5-7, 10-14, and 21 are pending in the application. Claims 1-4, 8, 9, and 15-20 have been cancelled. Claims 5-7, 10-14 and 21 stand rejected. No claims have been allowed.

IV. Status of Amendment

A "Response to Final Rejection" has been considered by the Examiner. No amendments to the specification or claims have been made subsequent to final rejection.

V. Summary of Invention

The present invention concerns a process for preparing antiviral pharmaceutical compounds. The compounds prepared by the process of the invention include the commercially valuable antivirals famciclovir and penciclovir. One claim (claim 5) is directed to a novel intermediate compound used in the process. The process of the invention uses a compound having a 6-chloro moiety as a starting material, i.e., 2-amino-6-chloropurine (or its amino-protected derivative). The process of the invention requires a specific sequence of steps which sequence is: coupling, decarboxylation, reduction and esterification, followed finally by removal of the 6-chloro substituent. Appellants have unexpectedly found that retention of the 6-chloro substituent during the various steps results in improved yields.

VI. Issues

A) Whether claim 5 is patentable under 35 U.S.C.§102(b) and 35 U.S.C.§103(a) over EP 302644.

B) Whether claims 6, 7, 10-14, and 21 are patentable under 35 U.S.C.§103(a) over EP 302644.

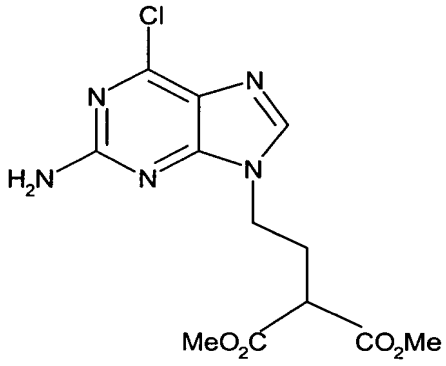
VII. Grouping of Claims

The appealed claims fall into these groups, namely claim 5 directed to a specific chemical compound, claims 6, 7, and 10-14 directed to a chemical process, and claim 21 directed to a chemical process that includes a transesterification step. These three groups of claims do not stand or fall together and separate arguments for patentability will be made for each group.

VIII. Arguments

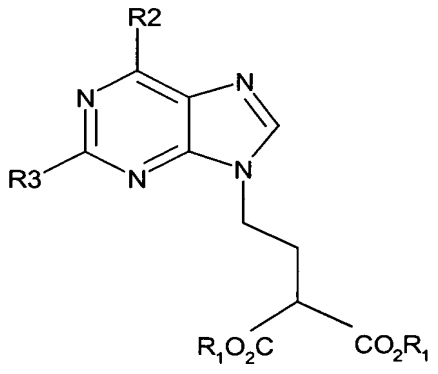
A) Claim 5 is patentable under both 35 U.S.C.§102(b) and 35 U.S.C.§103(a) over EP 302644.

The compound of claim 5 is



In the Final Rejection the Examiner rejected Claim 5 as being anticipated under 35 U.S.C.§102(b) by Formula (I) of EP 302644.

EP 302644 teaches Formula (I) to be a genus of compounds having the structure:



(I)

wherein

R_1 is C_{1-6} alkyl, or phenyl C_{1-6} alkyl in which the phenyl group is optionally substituted; R_2 is hydrogen, hydroxy, chlorine, C_{1-6} alkoxy, phenyl C_{1-6} alkoxy or amino; R_3 is halogen, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, azido, an amino group, or a protected amino group.

The Examiner's rejection on page 2 of the Final Rejection refers to Formula (I) of EP 302644 and the Examiner holds:

R_3 as amino is clearly preferred, as it is the sole choice seen in the final product. As for R_1, two choices are given as preferred at page 7, line 7, viz., methyl and ethyl. Claim 5 has the methyl. For R_2, there is a list on page 7, lines 8-9, which has 3 or 6 items in it, depending on how one counts, one of which is chloro.

There is no question that Formula I of EP 302644 with its broad definitions of R_1, R_2 and R_3 encompasses far too many compounds to anticipate Appellant's claimed compound. What is in question is whether the subgeneric compound constructed by the Examiner allegedly from the "preferences" taught by EP 302644 is legitimate. It is respectfully submitted that the fabricated subgeneric is not proper and, therefore, Appellant's claimed compound is not anticipated.

Regarding R_1, in the Final Rejection the Examiner points to page 7, line 7, of EP 302644 which states: "Values for R_1 in compounds of formula (I) include C_{1-4} alkyl, for example methyl and ethyl." It is respectfully pointed out that although methyl and ethyl are the only specific moieties mentioned, they are not indicated as preferred, they are listed as merely examples. C_{1-4} alkyl includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

Regarding R_2, in the Final Rejection on page 2 the Examiner states that on page 7, lines 8-9 of EP 302644 there is a list "which has 3 or 6 items in it, depending on how one counts, one of which is chloro." EP 302644 specifically teaches "Values for R_2 in compounds of formula (I) include hydrogen, chlorine, and C_{1-4} alkoxy, for example methoxy." As methoxy is only illustrative, use of C_{1-4} alkoxy encompasses more than 8 possibilities, in addition to the first 2.

Regarding R_3, it is stated in the Final Rejection that "R_3 as amino is clearly preferred, as it is the sole choice seen in the final product." (Final Rejection, page 2). It is respectfully submitted that this statement is incorrect. For the final compound of EP 302644 (i.e., Compound A), amino is clearly preferred – in fact it is required – but in the context of Compound I or Compound II, synthetic intermediates for preparing Compound A, no such teaching exists. On page 7, lines 12-13 of EP 302644, it is stated that:

> Suitable values for R_3 when a protected amino group include C_{2-5} alkanoylamino such as acetylamino or pivaloylamino, aroyl such as benzoyl, and arylmethyl such as benyzl.
>
> Values for R_3 in compounds of formula (I) include amino, halogen for example chlorine, and protected amino such as C_{2-5} alkanoylamino, for example acetylamino.

Further, on page 6, lines 51-54, of EP 303644, converting R_3 to amino is disclosed as a particular embodiment. Nowhere does EP 303644 teach that amino is preferred, only that having R_3 as amino in Compound I is one way to arrive at Compound A.

There may be many reasons why substituents other than amino for R_3 may be preferred, e.g., a skilled artisan may consider the presence of an amino group in a chemical intermediate that is going to undergo further conversion as undesirable, as it may be readily amenable to undesirable chemical modification in a later reaction. If anything, EP 303644 in the passage quoted above teaches that protected amino is preferred. Regarding pinning a specific number on the possibilities of R_3 substituents as the Examiner in wont to do, this is not possible because "protected amino" is not defined with such precision to allow placing metes and bounds on the number of possibilities.

In the Advisory action on page 2 it is stated that "using the named choices (without any reference to preference) for R_1, R_2 and R_3 , 2 x 3 x 7 = 42". The Examiner is taking the position that fabricating a subgeneric for anticipation purposes in valid if one uses only the moieties specifically named. Appellant is aware of no such authority which allows this. In the list of R_2 substituents in lines 29-30 on page 8 of EP 302644, "phenyl C_{1-4} alkoxy" is also named, but no specific example is given; does this mean that it should be ignored? Following the Examiner's reasoning the answer would be "yes", which Appellant maintains is manifestly not the case. Rather than use only the specifically named substituents, why not use only the ones actually exemplified? Appellant is not advocating that this should be done, but if it were, there is no example with R_2 as chloro, therefore, Appellant's compound could not be anticipated. The Examiner cites In re Petering 133 USPQ 275; In re Sivaramarishnan 213 USPQ 441; and In re Schaumann 197 USPQ 5. to support the 102 rejection, but does not cite In re Ruschig 145 USPQ 274 or In re Arkley 172 USPQ 524. None of these cases hold that a rigid formula must be used to define anticipation (e.g., if a generic structure has 42 possibilities, then it anticipates all members of the genus). Rather, all of these cases hold that the total circumstances of an individual situation must be considered. One of the factors considered in these cases is the how closely related the moieties are, for example, the CCPA, concluding no anticipation, in In re Ruschig at page 282 states :

> ...we are not dealing with such closely related units as the H and CH_2 and the five hydroxyalkyl components in Petering but with such widely differing , R_2 choices as *p*-acylaminobenzene, diphenyl, β-naphthalene and dimethylbenzene...

Similar to In re Ruschig, the "named" units for R_3 in EP 302644, are vastly divergent, e.g., hydrogen, amino, chlorine, acetylamino, pivaloylamino, benzoyl, and benzyl. Even for R_2, hydrogen, chlorine and methoxy are substantially different. In re Arkley warns against "picking and choosing" to concoct an anticipation rejection and it is submitted that this is precisely what has been done in the Final Rejection.

In summary regarding the rejection of Claim 5 under 35 U.S.C.§102(b), the Examiner has constructed a subgeneric compound within the scope of Compound I, allegedly from preferred definitions of R_1, R_2 and R_3 in the specification of EP 302644, which has been held to anticipate Appellant's Claim 5. Appellant submits that the subgeneric compound constructed by the Examiner is an invalid hindsight reconstruction of the prior art using Appellant's own disclosure as a guide, and such constructed subgeneric compound is not within the guidelines of In re Petering 133 USPQ 275; In re Sivaramarishnan 213 USPQ 441; In re Schaumann 197 USPQ 5, In re Arkley 172 USPQ 524), and In re Ruschig 145 USPQ 274.

Claim 5 also stands rejected 5 under 35 U.S.C.§103(a) over EP 302644. Regarding this obviousness rejection, if one were to follow the teachings of the working examples of EP 303644, not only would Appellant's Claim 5 not be anticipated, but it would be impossible to arrive at such a compound because the examples teach removal of the 6-chloro prior to decarboxylation (see the discussion, *infra*, regarding the process claims). Therefore, if one following the teachings of EP 302644 would find it impossible to arrive at Appellant's claimed compound, it follows that said compound cannot be obvious in view of EP 302644.

B) Claims 6, 7, 10-14 and 21 are patentable under 35 U.S.C.§103(a) over EP 302644

The rejected claims use a specific compound having a 6-chloro substituent as a starting compound, i.e., 2-amino-6-chloropurine (or its amino-protected derivative). The process of the invention requires a specific sequence of steps, which sequence is: coupling, decarboxylation, reduction and esterification, followed finally by removal of the 6-chloro substituent. Appellants have unexpectedly found that retention of the 6-chloro substituent during the various steps results in improved yields.

Claims 6, 7, 10-14 and 21 stand rejected under 35 U.S.C.§103(a) over EP 302644.

EPO 302644 discloses a bromotriester route. The bromotriester route is a process which has been found to be inconvenient for use on a large, commercial scale. A primary reason for such inconvenience is because it requires a chromatography separation of the N-

7 and N-9 isomers resulting from the addition/coupling reaction, Description 11 (page 15) of EP 302644. The present process was developed as an improvement in the bromotriester route in order to facilitate large scale commercialization of the process.

The process steps on pages 5 and 6 of EPO 303644 do not teach when the starting material, 2-aminochloropurine (ACP) is to be dechlorinated. The only guidance in EP 302644 is the specific examples directed to use of Formula (V) compounds which produce the final compound, Famciclovir. This bromotriester route discloses the following sequence of reactions:

a) coupling of triethyl 3-bromopropane-1,1,1-tricarboxylate (formula (V)) to 2-amino-6-chloropurine (formula (II)) (Description 11);

b) removal of the 6-chloro substituent (R_2) (Description 12);

c) decarboxylation (Example 3);

d) reduction (Step A(b)); and

e) *O-acetylation* (Step A(c)).

However, in order to dechlorinate the tricarboxylate intermediate in Description 12, the compound is first isolated. This isolation, due to the process conditions used, and the additional impurities produced by this process, etc., requires 7 additional steps.

In contrast, the present process does not require these isolation steps, and further does not produce 2 of the additional impurities of the EP 302644 process.

The present invention requires the following steps:

a) coupling of compound of formula (V) with a compound of formula (II) to yield a compound of formula (VI) (Example 1);

b) decarboxylation (Example 1) (to give Compound 5, Annex 3);

c) reduction (Example 2);

d) O-acetylation (Example 2); and

e) removal of the 6-chloro substituent (R_2) (Example 3).

The teachings of EPO 302644 would not lead the skilled artisan to carry out the sequence of steps as presently claimed herein, i.e., coupling, decarboxylation, reduction and esterification, followed finally by removal of the 6-chloro substituent. Thus it is submitted that EP 302644 does not teach or suggest Appellant's claimed process and, therefore, a valid case of *prima facie* obviousness has not been made out. Nevertheless, even assuming, *arguendo*, that a valid *prima facie* case of obviousness has been made out, it is submitted

that the unexpected results achieved by retention of the 6-chloro throughout the claimed process as shown in Appellant's specification and submitted declarations rebut any *prima facie* case of obviousness made out by the Examiner.

To support the patentability of the claimed process, Appellant submitted two Declarations during prosecution. They are the Geen Declaration which is attached hereto as Appendix B and the Jones Declaration which is attached hereto as Appendix C.

The Geen Declaration and schemes 1 and 2 on pages 5 and 6 of the specification demonstrate that the bromotriester process described in EP 302644 produces an overall yield of about 11%, whereas the instant process produces an overall yield of about 41%. The significant improvement in overall yield comes from not one step which benefits from the 6-chloro retention but from two different process steps.

These particularly advantageous and unexpected features of the present invention resulting form retention of the chlorine in the chemical intermediates are not taught or suggested in EP 302644. A skilled artisan would not be directed to the improved benefits of yield in the decarboxylation step, nor to the improved yields in the reduction and acetylation steps.

The Examiner, however, holds that these unexpected effects are unpersuasive for the reasons enunciated in the Office Action dated June 14, 1999. Essentially three reasons are given (A-C) which are as follows:

> A. The difference might have arisen from a different decarboxylation process. The prior art process (ex. 3) used NaOEt at room temperature. Applicants used NaOMe under cooling. Applicant's considerably better yield might have arise from that. Note that this point applies event to claim 20, insofar as the temperature aspect of it is not reflected in the claim 20 limitations.
>
> B. Similarly, the reduction with $NaBH_4$ was also done differently. The prior art used elevated temperatures and refluxing t-butanol. Applicants used CH_2Cl_2 with cooling, and perhaps that is what accounted for the better yields.
>
> C. Another important difference is in the coupling step, which is especially relevant because the coupling step is identical in EP 302644 and the claims. This step (Description 11 in EP 302644) involves the exact same materials and goes in 56% yield, whereas Applicants presumably got something in excess of 70% yield. This may have arisen from the fact that Applicant did the reaction for longer and at a higher temperature (40°C vs. 60°C - 63°C), and so the prior art may simply not have

> gone to completion. At any rate, this coupling step cannot properly be part of the yield comparison because at this point, the process is identical to that of the prior art working example. Or perhaps this significant difference in yield arose from a more efficient workup.

The comparative examples in the Jones Declaration directly addresses the objections raised by the Examiner in his action dated June 14, 1999 (page 6, points A-C). The Examiner alleges that the advantages obtained using the process of the invention may not be due to the presence of the chloro until after the decarboxylation step as claimed, but may be due to the different reagents, temperatures, etc. highlighted in points A-C.

The Jones Declaration compares the two processes, i.e., the process claimed by Appellant wherein the chlorine is removed at the end versus the process of EP 302644 wherein the chlorine is removed earlier (after the coupling of triethyl 3-bromopropane-1,1,1-tricarboxylate to 2-amino-6-chloropurine). The results show that the overall yield of the instant process is 41% of a crystalline solid, representing a 41% yield of usable famciclovir, i.e., famciclovir of a pharmaceutically acceptable quality, which is in comparison to an overall yield of 14% of a crude brown oil representing a 0% yield of usable famciclovir from the prior art process.

These data clearly indicate that the continued presence of the 6-chloro substituent during decarboxylation and through to the final step of the process is responsible for the advantages of the instant process over that process as described in the '644 patent.

The Examiner in the Advisory Action refers back specifically to the paper of August 16, 2000. The Examiner is critical of the Jones Declaration and specifically states:

> The Declaration has four major flaws.
>
> First, it does not properly replicate the prior art process for Stage 1, step 3, the decarboxylation of the triester, and second, it provides a version of the claimed process which does not fall within claim 10. In EP 302644, the process is set forth in Example 3, i.e., the conversion of D12 (prepared in Description 12) to E3. This process appears as step 3 on page 5 of the declaration, as is described on page 6, beginning on line 3. There are three significant differences:
>
> A. EP 302644 uses NaOEt in ethanol; the Declaration uses NaOMe in methanol. Thus, not only is a different reagent used for the decarboxylation itself, but a transesterification is also being done. Note that in the reference, the

conversion of D12 to E3 is not a transesterification, as one goes from the ethyl ester of D12 to the ethyl ester of E3. Further, note that the claims do not require a transesterification either and indeed make no mention of transesterification, as they simply call the process a decarboxylation. As a result, the process as set forth in the Declaration does not even fall within claim 10. Thus, a proper comparison in the Declaration would have used NaOEt in ethanol in both the EP 302644 and the claimed process.

B. EP 302644 acidifies the mixture to pH 3 prior to solvent evaporation. The Declaration process has no such step.

C. EP 302644 purified the material, including a drying process, which converted the yellow oil to a crystalline solid. No such process occurs in the Declaration.

Third, the reduction (Stage 2, step 1) in the EP 302644 process was done differently from what appears in the actual reference on page 18, step a). (The Examiner assumes that the "6-Chloro" at the sixth from last line of page 6 of the Declaration is a typographical error).

D. In EP 302644, the reduction is done in t-butanol; in the Declaration, in methylenedichloride.

E. In EP 302644, the reduction is done at reflux; in the Declaration it is done at 20°C.

F. In EP 302644, the methanol addition was done without chilling; in the Declaration, the reaction mixture was chilled to keep it at room temperature.

G. In EP 302644, the product is purified by chromatography before the acetylation; this step does not occur in the Declaration. This is potentially important because the product is described in EP 302644 as being a white solid, whereas in the Declaration it is described as being yellow colored. This means that it is likely that the EP 302644 process produced a purer product than the Declaration process, vitiating the comparison.

Fourth, the acetylation of the diol (Stage 2, step 2) in the EP 302644 process was done differently than what actually appears in the reference on page 19, step c):

H. In EP 302644, there was used THF as solvent alone with pyridine. In the Declaration, there was

used methylenedichloride as solvent plus triethylamine.

I. The workup was completely different. For example, in EP 302644, there was a drying process and column chromatography; neither was seen in the Declaration.

As a result of all these differences, Applicants cannot be considered to have done a proper replication of the reference. It must be noted that the EP 302644 reference starts where the Declaration starts, and ends with the same diacetylated diol, yet Applicants ended with a brown oil which they were unable to crystallize from n-butanol, whereas the EP 302644 reference states that they were able to obtain colorless crystals from n-butanol, melting at 102°C. It seems clear that these variations prevented a proper obtention of the results seen in EP 302644. The conclusion that the prior art process yields only a useless brown oil is directly contradicted by the fact that the EP 302644 did in fact produce the compound as colorless crystals of the correct melting point.

In the comparative synthesis presented in the accompanying Jones Declaration the same reduction conditions were used for the "EP 302644 type process" as for that described in the application under examination, namely reduction of the methyl ester to the corresponding diol using $NaBH_4$, in dichloromethane at 20°C. See paragraph 4, Stage 2, step I and paragraph 6, Stage 2, step I of the Declaration.

The Examiner asserts in the Advisory Action that "as a legal matter, applicants must compare to the prior art process." Appellant submits that this is an inaccurate statement. Convincing evidence of unobviousness can take many forms. As stated by the CCPA in In re Yan 175 USPQ 96 :

> To the extent that Appellant argues that it is not mandatory in every case to compare a claimed process with a prior art process in their entireties in order to establish the patentability of the claimed process, we surely agree with him. What is required as convincing evidence in given case depends entirely on the proposition sought to be proved by that evidence. (In re Yan at 98)

The experiments performed in the Jones Declaration were designed to determine the significance of the continued presence of the 6-chloro substituent during carboxylation and through the final step. The proposition sought to be proved does not require an exact duplication of the examples of EP 302644 in the most minute detail. The Jones Declaration

compares two routes to the desired product which differ only in that one removes the Cl prior to decarboxylation as in EP 302644 and the other removes the Cl after decarboxylation as in the present invention. The fact that a different solvent, temperature, etc. may have been used relative to EP 302644 does nothing to compromise the scientific validity of the conclusion reached, i.e., that continued presence of the 6-chloro substituent during carboxylation and through the final step results in an unexpected yield increase. The point at which the chloro substituent was removed was the only difference, i.e., the comparison was scientifically valid.

Moreover, Dr. Jones, an expert in the art, concludes in paragraph 9 of his declaration that his "experimental data confirm that the continued presence of the 6-chloro substituent during decarboxylation and through the first step of the process is responsible for the advantages of the process of '926 over that described in '644 rather than (sic) the particular reaction conditions employed..." Such a statement is an opinion of an expert interpreting data and thus should be accorded appropriate weight. The results presented show unambiguously that the advantages are due to the Cl substituent and not due to any other conditions as all other conditions were the same.

The Examiner's comments pointing out that the process of EP 302644 gave a crystalline product yet the process in our declaration gave a useless brown oil only further highlights the surprising advantages obtained using the process of the invention. In particular, it supports the arguments previously presented that the process of the invention allows for the production of a pure product in high yield without the need for the chromatographic purification steps, which were necessary in EP 302644 (using the reaction conditions as we now claim, not as compared).

The Examiner also alleges that the process in the Jones Declaration is not valid because it includes a transesterification which is not within the scope of Appellant's claims. The process of the Jones Declaration does fall within claim 10 as a decarboxylation, i.e., removal of -CO2Et, does take place, the fact that the conditions chosen also results in a transesterification of the 2 remaining -CO2Et groups is irrelevant as claim 10 recites " ... which process comprises ... ".

Furthermore, as acknowledged by the Examiner, EP 302644 does not teach a transesterification step. Appellant's Claim 21 requires "decarboxylation with sodium methoxide in methanol", which results in transesterification, i.e., replacing the ethyl esters with methyl esters. Therefore, Appellant requests that the patentability of Claim 21 be

considered separately from the other claims because it contains a feature not taught by EP 302644, and nothing has been cited which would suggest such a feature.

In summary, The particularly advantageous and unexpected features of the present invention are not taught, nor are they suggested in EP 302644 . The skilled artisan would not be motivated by the '644 reference to retain the chlorine in the chemical intermediates. A skilled artisan would not be directed to the improved benefits of yield in the decarboxylation step, nor to the improved yields in the reduction and acetylation steps. Appellant's claimed method comprises a specific sequence of steps simply not taught or suggested by EP 302644. The sequence claimed herein involves coupling, decarboxylation, reduction, and esterification, followed finally by removal of the 6-chloro substituent.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6765

Thomas R. Savitsky
Attorney for Applicant
Reg. No. 31,661

TRS/ld

Date: October 22, 2001

APPENDIX A

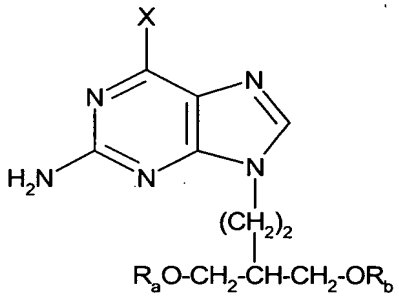
The Claims on Appeal

5. 2-Amino-6-chloro-9-(methyl-2-carbomethoxybutanoate-4-yl)purine.

6. A process according to claim 10 for the preparation of 9-(4-acetoxy-3-acetoxymethylbut-l-yl)-2-aminopurine (famciclovir).

7. A processing according to claim 10 for the preparation of 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine (penciclovir).

10. A process for the preparation of a compound of formula (A):

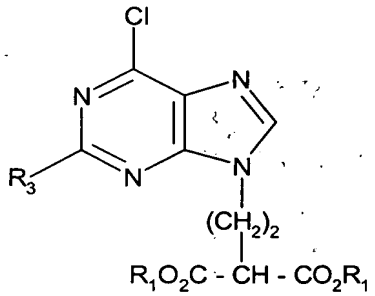


(A)

wherein:

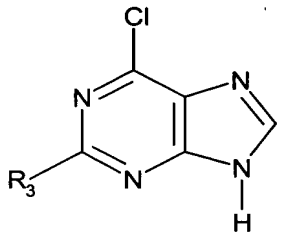
X is hydrogen or hydroxy; and R_a and R_b are hydrogen or acetyl, which process comprises:

(i) the preparation of a compound of formula (I):



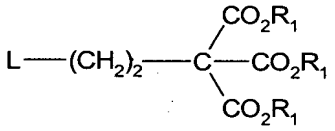
(I)

wherein R_1 is C_{1-6} alkyl, or phenyl C_{1-6} alkyl in which the phenyl group is optionally substituted; and R_3 is an amino group or a protected amino group, which preparation comprises the reaction of a compound of formula (II):



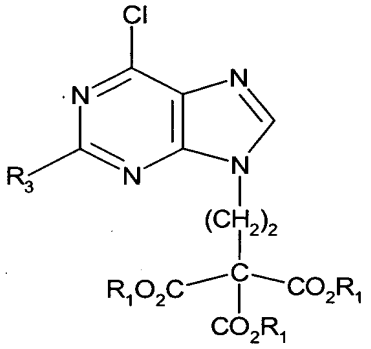
(II)

wherein R_3 is as defined above for formula (I), with a compound of formula (V):



(V)

wherein L is a leaving group and R_1 is as defined for formula (I), to give a compound of formula (VI):



(VI)

and thereafter converting the intermediate compound of formula (VI) to a compound of formula (I) via decarboxylation; and

(ii) conversion of the resulting compound of formula (I) to a compound of formula (A) by:

a) removal, if necessary, of the amino protecting group;

b) reducing the ester groups CO_2R_1 to CH_2OH groups, and, if necessary, acetylating to form the corresponding CH_2Oac groups; and

c) dechlorinating via a hydrogenolysis reaction to yield a compound of Formula (A) in which X is hydrogen; or dechlorinating via a hydrolysis reaction to yield a compound of Formula (A) in which X is hydroxy.

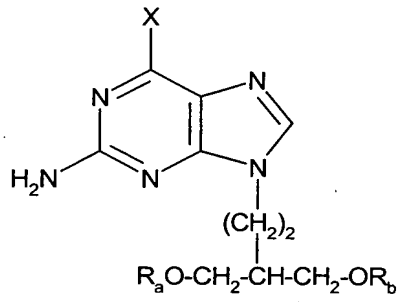
11. A process according to claim 10 wherein, in the compound of Formula (V), R_1 is C_{1-6} alkyl and L is halogen.

12. A process according to claim 11, wherein L is bromo.

13. A process according to claim 10, wherein R_1 is methyl or ethyl.

14. A process according to claim 10 wherein decarboxylation of the compound of formula (VI) is effected by the addition of about 0.42 equivalents of sodium methoxide.

21. A process for the preparation of a compound of formula (A):

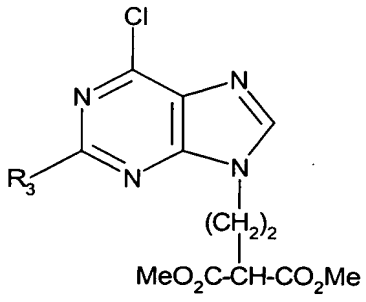


(A)

wherein

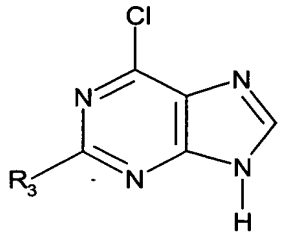
X is hydrogen or hydroxy; and R_a and R_b are hydrogen or acetyl, which process comprises:

(i) the preparation of a compound of formula (I):



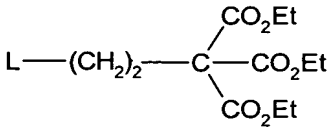
(I)

wherein R_3 is an amino group or a protected amino group, which preparation comprises the reaction of a compound of formula (II):



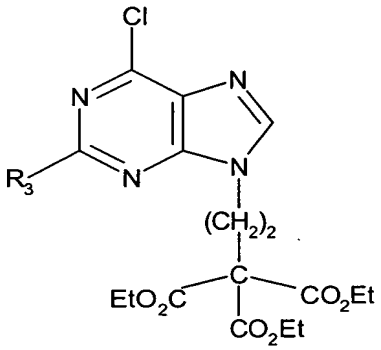
(II)

wherein R_3 is as defined above for formula (I) with a compound of formula (V):



(V)

wherein L is a leaving group, to give a compound of formula (VI):



(VI)

and thereafter converting the intermediate compound of formula (VI) to a compound of formula (I) via decarboxylation with sodium methoxide in methanol; and

(ii) conversion of the resulting compound of formula (I) to a compound of formula (A) by:

a) removal, if necessary, of the amino protecting group;

b) reducing the ester groups CO_2Me to CH_2OH groups, and, if necessary, acetylating to form the corresponding CH_2OAc groups; and

c) dechlorinating via a hydrogenolysis reaction to yield a compound of Formula (A) in which X is hydrogen; or dechlorinating via a hydrolysis reaction to yield a compound of Formula (A) in which X is hydroxy.

APPENDIX B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Dales
Serial No:	08/732,479
For:	Preparation of Purines
Art Unit No.:	1611
Examiner:	Mark L Berch

DECLARATION OF GRAHAM RICHARD GEEN

I, Graham Richard Geen, hereby declare:

1. That I am Graham Richard Geen of SmithKline Beecham p.l.c., New Frontiers Science Park, Harlow, Essex, CM19 5AW, United Kingdom. I was awarded an honours degree of Bachelor of Science (Chemistry) in 1973 and the degree of Doctor of Philosophy in 1979, both from the University of Bristol. Since 1979 I have been employed by Beecham Group p.l.c. and SmithKline Beecham p.l.c. in various capacities relating to medicinal and synthetic chemistry, having spent 14 years working in the antiviral field. At the present time, I am an Assistant Director in the Department of Synthetic Chemistry. I am responsible for the work of 7 graduate chemists. I am an author or co-author of over 25 scientific publications and presentations.

2. I am familiar with the present application US Serial No. 08/732,479 ('479), which relates to a process for the production of purines, e.g. famciclovir and penciclovir. I am also familiar with European Patent Application No. 302644 ('664) filed 25 July 1988, for which I am named as joint inventor.

3. '644 discloses a process for the production of purines of formula (A) using as starting materials a purine derivative of formula (II), e.g. 2-amino-6-chloropurine (ACP), and a tricarboxylate of formula (V). The desired compound of formula (A) does not contain a 6-chloro substituent, but a hydrogen. The process shown in '644 uses ACP as a starting material, but does not indicate when the chlorine should be removed to yield the desired dechlorinated final product of Formula (A). The only guidance regarding removal of the 6-chloro substituent in the '644 application is provided for in the

exemplified production of famciclovir. This process uses the following sequence of reactions, see Annex 1:

a) coupling of triethyl 3-bromopropane-1,1,1-tricarboxylate (formula (V)) to 2-amino-6-chloropurine (formula (II)) (Description 11);
b) removal of the 6-chloro substituent (R_2) (Description 12);
c) decarboxylation (Example 3);
d) reduction (Step A(b)); and
e) *O*-acetylation (Step A(c)).

4. The coupling step a) of '644 produces not only the desired N-9 isomer (Compound 1, Annex 2) and the unwanted N-7 isomer (Compound 2, Annex 2), but also smaller amounts of the corresponding N-9 and N-7 diesters (Compounds 3 and 4, Annex 2) which result from *in situ* decarboxylation. The process of '644 is inconvenient for use on a large, commercial scale, because it requires chromatographic separation of the desired N-9 isomer and unwanted N-7 isomer. In addition to suppressing the yield of the desired N-9 isomer (Compound 1, Annex 2, the presence of the N-9 and N-7 diesters (Compounds 3 and 4, Annex 2) further complicates the isolation of the N-9 isomer since 4 products are present in the reaction mixture. Hence in Description 11 the isolation procedure for Compound 1, Annex 2, involves numerous steps, viz:

i) removal of N,N-dimethylformamide;
ii) addition of ethyl acetate, washing and drying;
iii) removal of ethyl acetate;
iv) recrystallisation from butan-1-ol;
v) evaporation of butan-1-ol from filtrate;
vi) column chromatography of filtrate residue; and
vii) evaporation of eluant.

5. The process of '479, which was invented during attempts to facilitate large scale commercial production of purines of formula (A), uses the following sequence of reactions, see Annex 3:

a) coupling of compound of formula (V) with a compound of formula (II) to yield a compound of Formula (VI) (Example 1);
b) decarboxylation (Example 1) (to give Compound 5, Annex 3);
c) reduction (Example 2);
d) *O*-acetylation (Example 2); and
e) removal of the 6-chloro substituent (R_2) (Example 3).

Notably, in this process the 6-chloro substituent remains in place until the final step of the synthesis instead of being removed after the coupling step a) as in '644.

6. In the process of '479 the triethyl ester (VI) is converted without isolation to the dimethyl ester, Formula (I), this N-9 isomer is then selectively precipitated from solution, free of the unwanted N-7 isomer. The process of '479 thus avoids the problems encountered in '644 since the presence of the 6-chloro substituent allows the N-9 isomer to be selectively precipitated from the N-7 isomer, and decarboxylation of the entire

reaction mixture reduces the number of products from 4 to 2. The advantage offered by this process is illustrated by the fact that the coupling and decarboxylation steps of the '479 process give an overall yield of 65% whereas the decarboxylation step alone of '644 only gives a yield of 59%.

7. In the process of '479 the yield at each step, and the overall yield, is substantially improved compared with that obtained using the process of '644. The overall yield of the '479 process is 41% and the overall yield of '644 process is 10.6%. The improved yields of the present invention arise through the maintained presence of the 6-chloro substituent until the end of the synthesis.

8. A further advantage of the process of '479 is found in the reduction step, paragraph 5 (c) above, where the reaction mixture is worked up using an aqueous solvent. In this step, it was found that the 6-chlorodiol is in fact less soluble than the dechlorinated diol, thus allowing easy isolation of the acetylated intermediate of the '479 process (see Example 2). This advantage is illustrated by the fact that the reduction and *O*-acetylation steps of the '479 process give a yield of 70% whereas the reduction and *O*-acetylation steps of the '644 process give a yield of 50.5% x 67% = 33.8%.

9. To summarize, the continued presence of the 6-chloro substituent during decarboxylation and through to the final step of the process is particularly advantageous because it allows:

a) convenient separation of the N-9 and N-7 isomers without requiring chromatography; and

b) the presence of the 6-chloro substituent in the diol produced in the reduction step decreases the solubility of the diol allowing convenient isolation in an aqueous solvent.

These advantages could not have been predicted from the disclosure of '644.

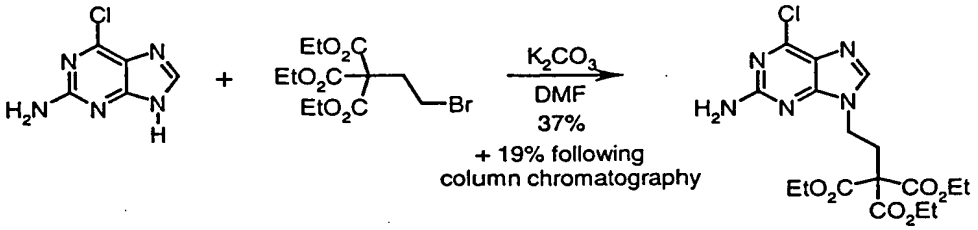
10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of this application or any patent issuing thereon.

Date: 15TH Dec 1999 G.R. Geen

Annex 1

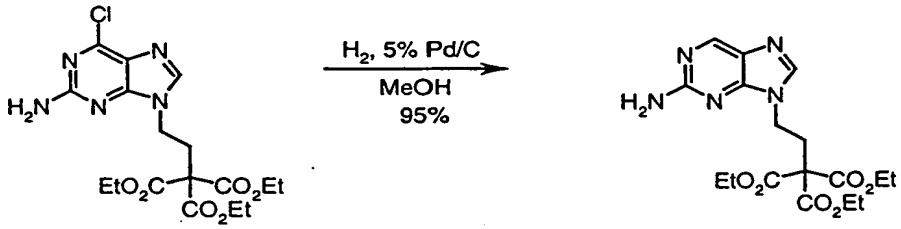
PROCESS FOR THE PREPARATION OF FAMVIR DISCLOSED IN EP 0 302 644 B1

Description 11

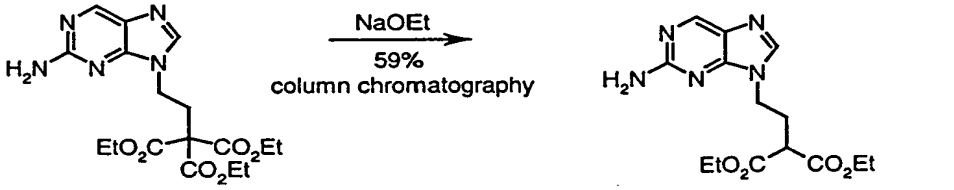


(reaction produces N-9 and N-7 triesters, plus smaller amounts of corresponding diesters)

Description 12

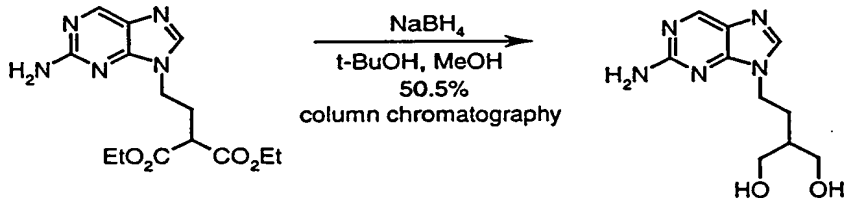


Example 3

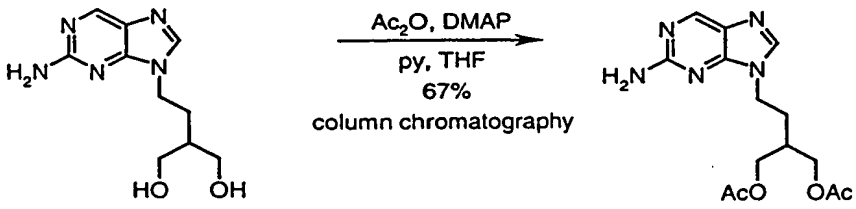


corresponding dimethyl ester is an oil
(see Example 1)

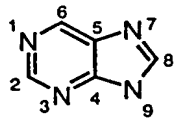
Preparation b) p.14

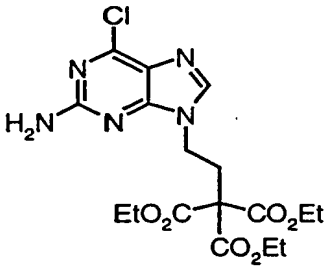


Preparation c) p.14

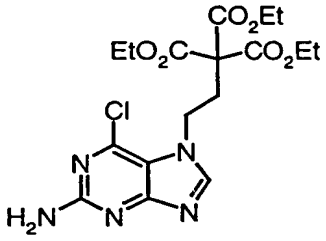


ANNEX 2

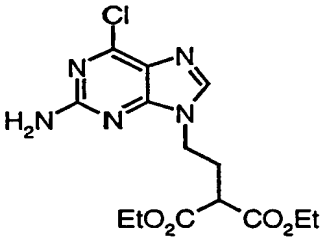




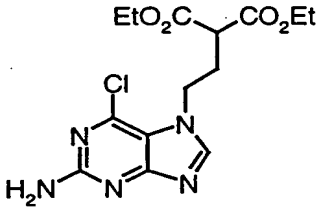
COMPOUND 1



COMPOUND 2



COMPOUND 3

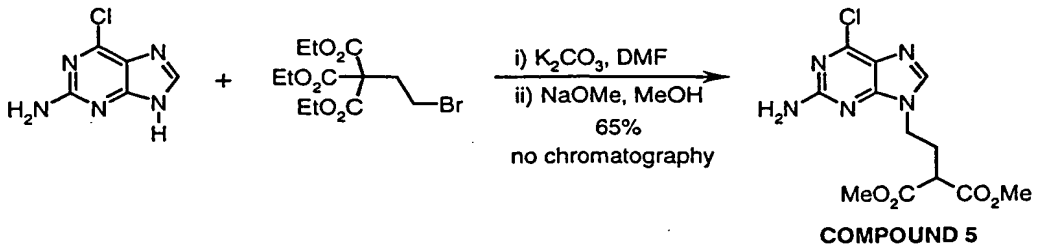


COMPOUND 4

ANNEX 3

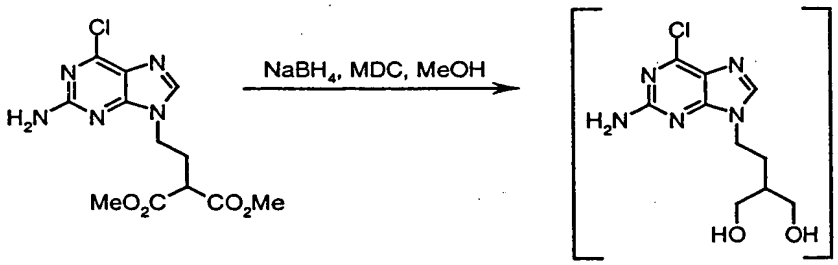
PROCESS FOR THE PRODUCTION OF FAMCICLOVIR DISCLOSED IN USSN 08/732,479

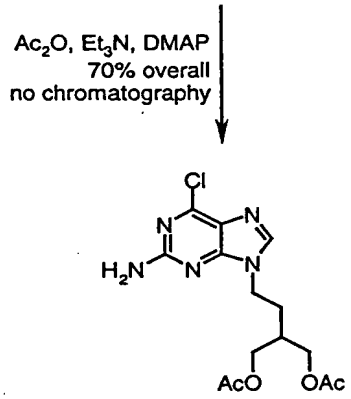
Example 1



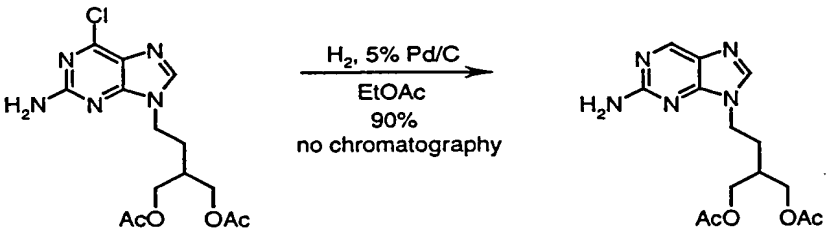
COMPOUND 5

Example 2





Example 3a



APPENDIX C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Dales
Serial No:	09/265,926
For:	Preparation of Purines
Art Unit No.:	1611
Examiner:	Mark L Berch

DECLARATION OF ALAN JONES

I, Alan Jones, hereby declare:

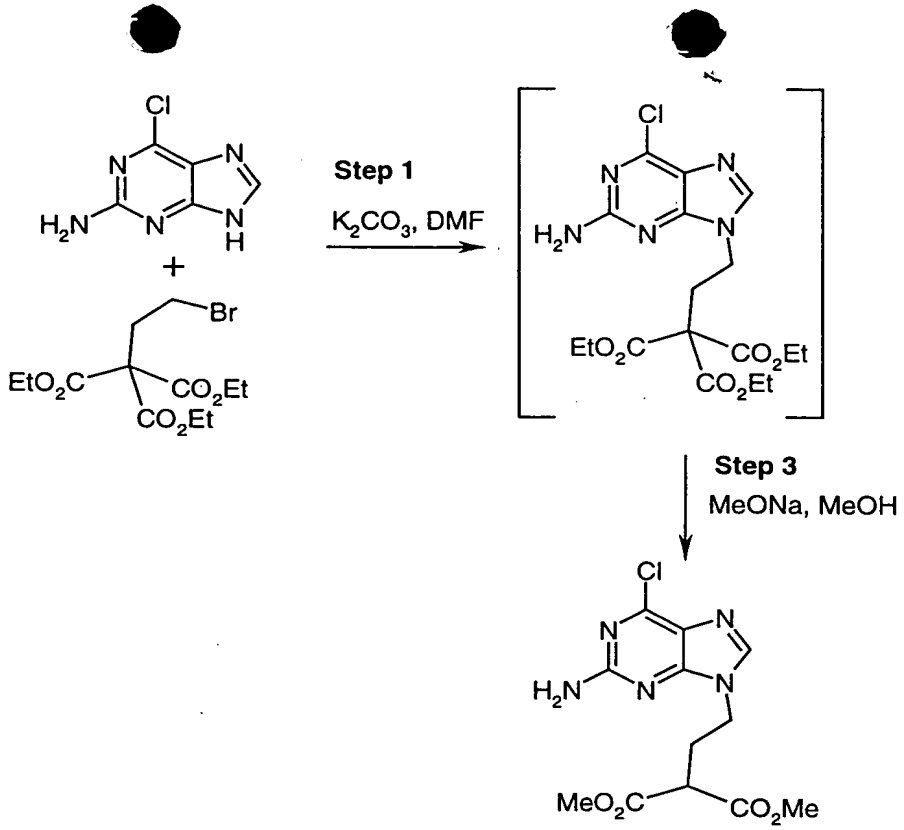
1. That I am Alan Jones of SmithKline Beecham p.l.c., Tonbridge, United Kingdom. I studied for a Bachelor of Science in Chemistry (1989) and a PhD in Organic Chemistry (1993) at the University of Manchester. Since 1993 I have been working for the pharmaceuticals business of SmithKline Beecham p.l.c. as an organic chemist within chemical development. At the current time I am an Investigator in the Synthetic Chemistry department. I am author or co-author of over 10 publications and presentations relating to organic chemistry.

2. I have read and understood the present application US Serial No. 09/265,926 ('926), which relates to a process for the production of purines, e.g. famciclovir and penciclovir. I have also read and understood European Patent Application No. 302644 ('644) filed 25 July 1988.

3. I understand that the process claimed in '926 differs from that exemplified in '644 in that the 6-chloro substituent is removed after the esterification of the 4-hydroxy-3-hydroxymethylbut-1-yl groups rather than after the coupling of triethyl 3-bromopropane-1,1,1-tricarboxylate to 2-amino-6-chloropurine.

4. The process described in '926 Examples 1-3(a) is shown below as Stage 1, steps 1 and 3 and Stage 2, steps 1 to 3 verbatim:

Stage 1



Step 1

Reaction of 2-amino-6-chloro purine with 4-bromo-2,2-bisethoxycarbonyl butyric acid ethyl ester

i) Mixture of 2-amino-6-chloro purine (9.18g, 53.1 mmol), triethyl 3-bromopropane-1,1,1-tricarboxylate (20.33g, 57.3 mmol), potassium carbonate (11.1 g, mmol) and N,N-dimethyl formamide (190 ml) were stirred together at 60-63°C for 22 hours.

ii) The hot reaction mixture was filtered through a bed of celite and the cake washed with DMF (30 ml).

iii) The combined filtrate and washings was evaporated by high vacuum distillation to give a red brown coloured oil.

Step 3

Decarboxylation and transesterification of triester

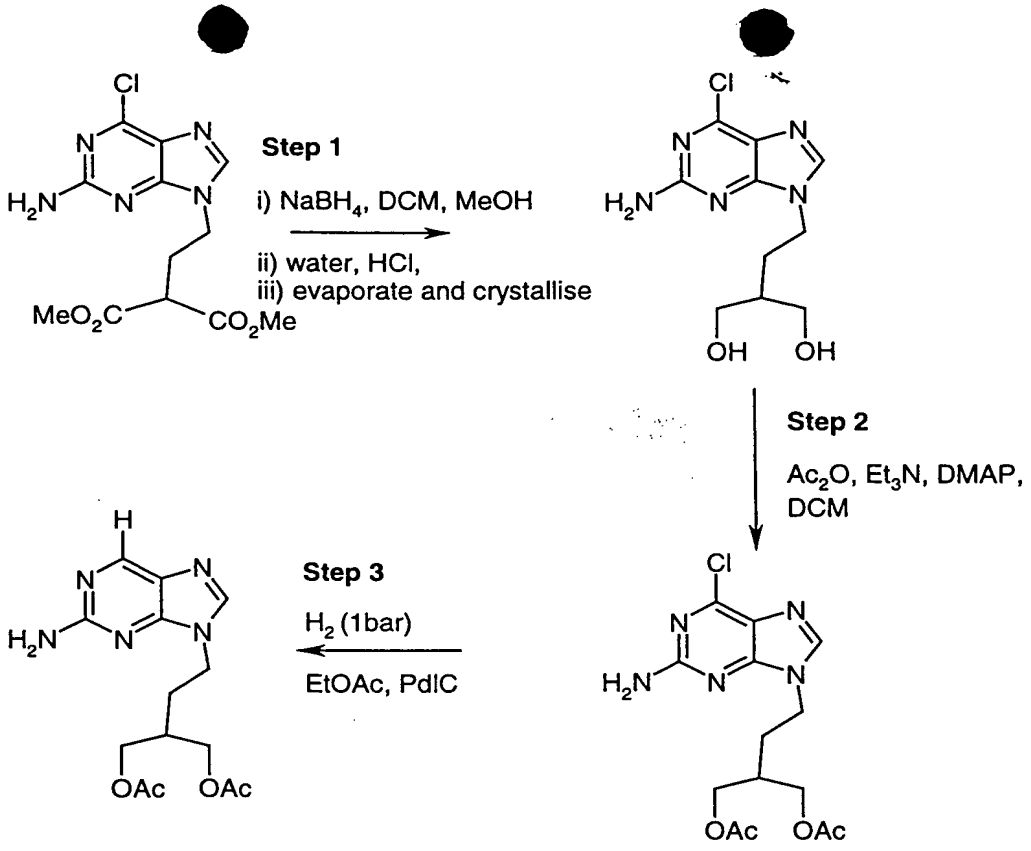
i) The product from **Step 1** was dissolved in methanol (140 ml) at 20°C and then a solution of sodium methoxide (1.20 g) in methanol (40 ml) was added with stirring.

ii) After 20 minutes a precipitate formed.

iii) The reaction mixture was cooled to 15°C and held at this temperature for 30 minutes

iv) The product was isolated by filtration and washed with methanol (10 ml) and dried at 40°C under vacuum. Weight yield 12.0 g of 95% purity.

Stage 2



Step 1

Reduction to diol

i) A mixture of 2-amino-9-(methyl 2-carbomethoxybutanoate-4-yl) purine (32.7 g), sodium borohydride (11.5 g) and dichloromethane (125 ml) was stirred at 20°C.

ii) Methanol (75 ml) was added over 2 hours maintaining a reaction temperature of 20-22°C

iii) The reaction mixture was left to stir for a further 1.5 hours.

iv) Water (100 ml) was added.

v) Concentrated hydrochloric acid (20-22 ml) was added dropwise to pH=6.7-7.0.

vi) Dichloromethane and methanol were removed by evaporation under vacuum until a volume of 150 ml remained.

vii) The precipitate was filtered and the cake washed with cold water (20 ml). Weight yield 30-40g.

Step 2

Acetylation of diol

i) The wet cake from **Step 1** (30-40g) was stirred with triethylamine (15 ml) and 4-N,N-dimethylamino pyridine (1 g) in dichloromethane (250 ml).

ii) Acetic anhydride (75 ml) was added dropwise over 20 to 30 minutes at such a rate to control the reflux.

iii) The reaction mixture was heated at reflux temperature for a further 1.5 hours.

iv) The reaction mixture was cooled to 20 °C and neutralised to pH=6.4-6.5 with 20% w/w sodium hydroxide solution.

v) The dichloromethane layer was separated and the aqueous phase extracted with dichloromethane (100 ml).
vi) The combined dichloromethane phases were evaporated to dryness.
vii) The crude damp solid was recrystallised from 3:1 methanol:water (75 ml), cooling the precipitate to 5°C for 1 hour before filtration.
viii) The product was washed with cold (0°C) 3:1 methanol:water (5 ml) and dried at 40°C in a vacuum oven. Weight yield 23g of 97-98% purity.

Step 3

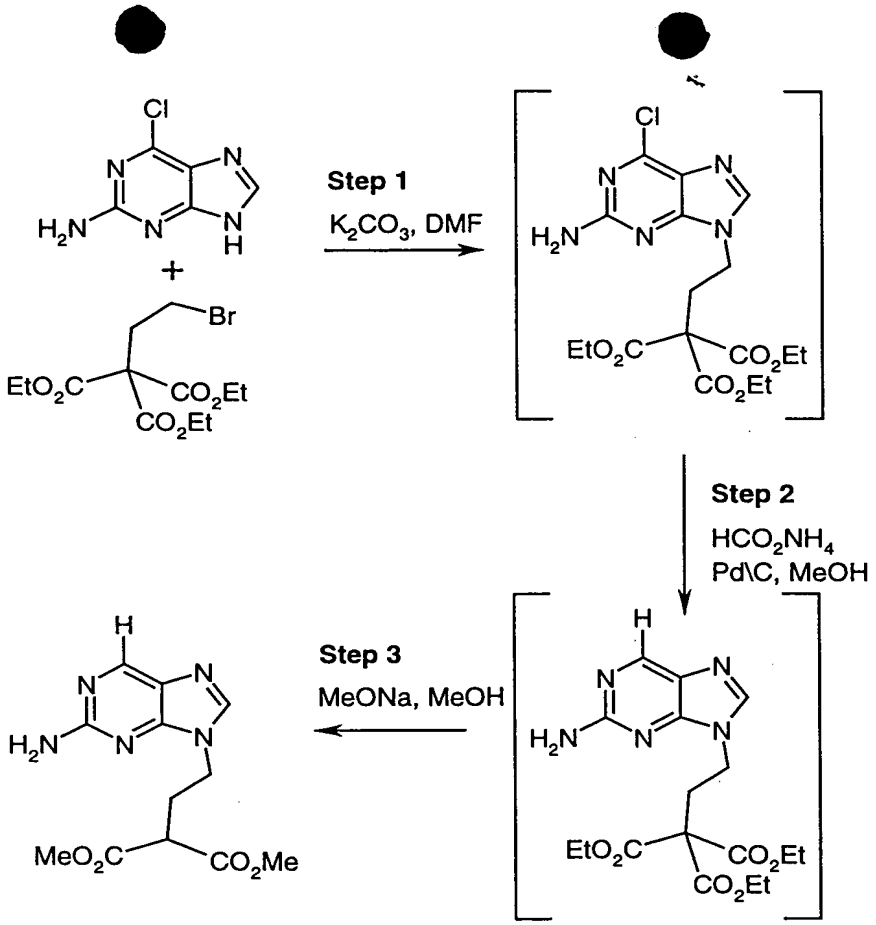
Hydrogenation of chloro purine

i) A mixture of 9-(4-acetoxy-3-acetoxymethylbut-yl)-2-aminopurine (15.4g), 5% palladium on carbon (6.16 g), triethylamine (6.6 ml) and ethyl acetate (77 ml) was stirred at 50°C under a hydrogen atmosphere at 1 bar pressure in an autoclave for 3-5 hours.
ii) The reaction mixture was washed out of the autoclave with ethyl acetate (30 ml) keeping the washings at 50°C.
iii) The reaction mixture and washings were filtered through a celite bed and the filter bed washed with ethyl acetate (30 ml).
iv) The combined filtrate and washings were evaporated to dryness to give a crude white solid.
v) The solid was recrystallised form n-butanol (62 ml), stirring the cooled solution at 0-5°C for 3 hours before filtration.
vi) The product was filtered off and washed with the mother liquors.
vii) The solid was re-slurried in n-heptane (50 ml), stirred for 30 minutes and filtered.
viii) The product was dried at 40°C for 16 hours under vacuum. Weight yield 11-11.3g.

5. I have now repeated the process described in '926 Examples 1-3(a) this time removing the 6-chloro as described in '644 after the coupling of triethyl 3-bromopropane-1,1,1-tricarboxylate to 2-amino-6-chloropurine (Stage 1, step 2), rather than after the esterification of the 4-hydroxy-3-hydroxymethylbut-1-yl groups (Stage 2, step 3). This process, which is referred to as the "EP302644 Type Process" differs from that described in '926 only at the dechlorination step, the remaining steps in the process use exactly the same reaction conditions as '926 thus allowing a direct comparison of the '926 and EP302644 Type Process.

6. The experimental details used for the EP302644 Type Process described in paragraph 5 is shown below as Stage 1, steps 1 to 3 and Stage 2, steps 1 and 2:

Stage 1



Step 1

Reaction of 2-amino-6-chloro purine with 4-bromo-2,2-bisethoxycarbonyl butyric acid ethyl ester

i) A mixture of 2-amino-6-chloro purine (9.18g, 53.1 mmol), triethyl 3-bromopropane-1,1,1-tricarboxylate (20.33g, 57.3 mmol), potassium carbonate (11.1 g, 80.3 mmol) and N,N-dimethyl formamide (190 ml) were stirred together at 60 to 63°C for 22 hours.

ii) The hot reaction mixture was filtered through a bed of celite and the cake washed with N,N-dimethyl formamide (30 ml).

iii) The combined filtrate and washings was evaporated by high vacuum distillation to give a red brown coloured oil. Weight yield 32.23 g.

Step 2

Hydrogenation of chloro purine

i) A mixture of crude 2-amino-6-chloro-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl) purine (32 g) prepared in **Step 1**, ammonium formate (30 g) and 5% palladium on carbon (6g) in methanol was heated at reflux under nitrogen for 2 hours.

ii) The reaction mixture was cooled.

iii) The mixture was filtered and the filtrate evaporated.

iv) The residues were dissolved in water (600 ml) and extracted with chloroform (3 x 300 ml) and the combined extracts dried over magnesium sulfate.

v) The drying agent was removed by filtration and the filtrate evaporated to give the product as a viscous yellow oil. Weight yield 17.87 g.

Step 3

Decarboxylation of triester

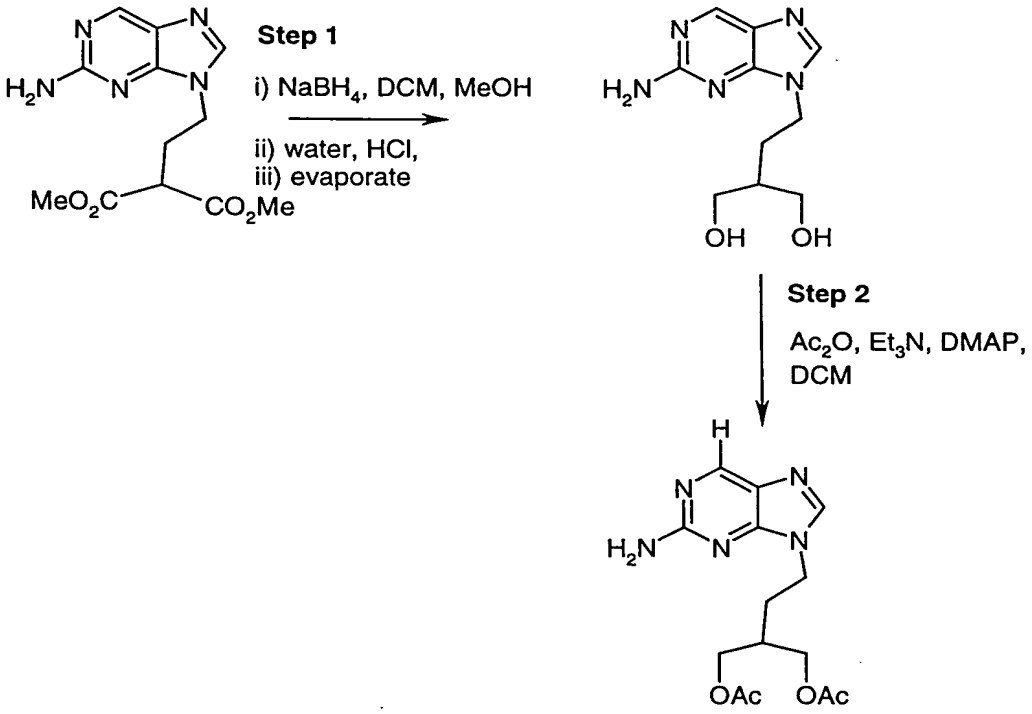
i) The product from **Step 2** (17.50 g) was dissolved in methanol (140 ml) at 20°C and then a solution of sodium methoxide (1.20 g) in methanol (40 ml) was added with stirring.

ii) The stirring was continued for 1 hour.

iii) No product crystallised from the reaction mixture. The reaction was a homogeneous yellow solution.

iv) The reaction mixture was evaporated to give a crude yellow coloured oily solid. Weight yield 14.79 g.

Stage 2



Step 1

Reduction of dimethyl ester.

i) A mixture of 2-amino-6-chloro-9-(methyl 2-carbomethoxybutanoate-4-yl) purine (14 g), sodium borohydride (4.90 g) and dichloromethane (54 ml) was stirred at 20°C.

ii) Methanol (32 ml) was added slowly over 2 hours maintaining a reaction temperature of 20-22°C with intermittent cooling with an ice/water bath.

iii) The reaction mixture was left to stir at ambient temperature for a further 1.5 hours.

iv) Water (43 ml) was added.

v) The reaction mixture was neutralised by dropwise addition of concentrated hydrochloric acid (approx. 9 ml) to pH=6.9 maintaining an internal temperature of 20-22°C.
vi) Dichloromethane and methanol were removed by evaporation under vacuum until a volume of 65 ml was obtained.
vii) The mixture was cooled to 5°C and stirred at this temperature for 30 minutes.
viii) The reaction mixture was stirred at 0-5°C for a further 1 hour.
ix) No precipitate formed and the reaction mixture was evaporated to dryness to give a crude yellow coloured solid. Weight yield 21.06 g.

Step 2

Acetylation of diol.

i) The crude solid from **Step 1** (20.5 g) was stirred with triethylamine (6.5 ml) and 4-N,N-dimethylamino pyridine (0.43 g) in dichloromethane (110 ml).
ii) Acetic anhydride (32 ml) was added dropwise over 20 minutes.
iii) The reaction mixture was heated at reflux temperature for a further 1.5 hours.
iv) The reaction mixture was cooled to 20 °C and neutralised to pH=6.4 with 20% w/w sodium hydroxide solution.
v) The dichloromethane layer was separated and the aqueous phase extracted with dichloromethane (45 ml).
vi) The combined dichloromethane phases were evaporated to dryness.
vii) The resulting crude oil did not crystallise from n-butanol or from methanol/water mixtures.

7. The processes of paragraphs 4 and 6 are summarised for comparative purposes in the Annex.

8. The overall yield of the process of '926 is 41% of a crystalline solid representing a 41% yield of usable famciclovir, i.e. famciclovir of a pharmaceutically acceptable quality. In comparison the overall yield of the corresponding process wherein the 6-chloro substituent is removed after the coupling of triethyl 3-bromopropane-1,1,1-tricarboxylate to 2-amino-6-chloropurine is 14% of a crude brown oil representing a 0% yield of usable famciclovir.

9. These experimental data confirm that the continued presence of the 6-chloro substituent during decarboxylation and through to the final step of the process is responsible for the advantages of the process of '926 over that described in '644 rather then the particular reaction conditions employed such as removal of the column chromatography steps or the nature of the ester obtained following decarboxylation of the compound of formula (VI).

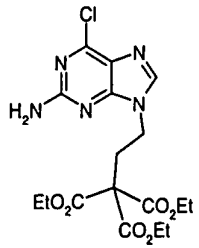
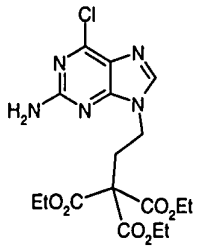
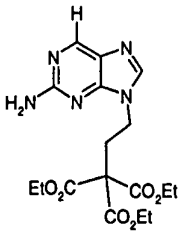
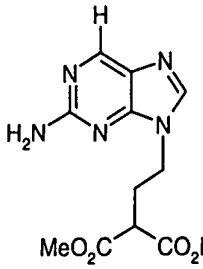
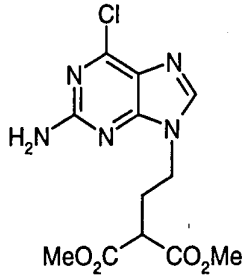
10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

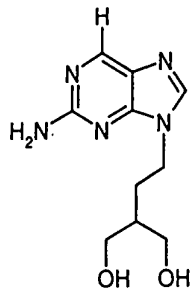
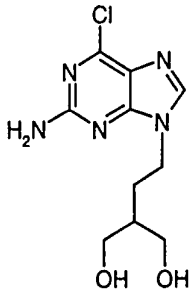
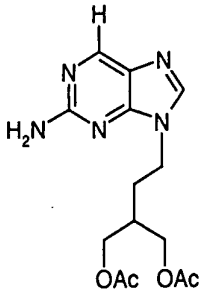
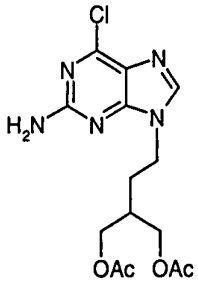
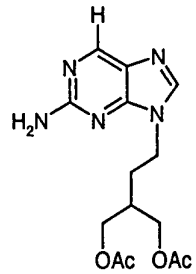
United States Code and that such wilful false statements may jeopardise the validity of this application or any patent issuing thereon.

Date: 20th December 1999

ALAN JONES

ANNEX

	"EP 302644 Type Process"			US 09/265,926		
Stage Number	Product	Comments		Product	Comments	
Stage 1 Step 1		Yield	32.23 g		Yield	Not given
		Form	Red/brown oil		Form	Red oil
Step 2		Yield	17.87 g	Not Applicable		
		Form	Viscous oil			
Step 3		Yield	14.79 g		Yield	12.0 g (65%)
		Form	Yellow oily solid		Form	Crystalline solid
	N9 and N7 were not separated. Purity Approx 45% by NMR				Assay 95%, selective crystallisation of N9 isomer	

Stage 2 Step 1		Yield	21.06 g		Yield	Quantitative wet cake
		Form	Yellow oily solid		Form	Wet cake
		Evaporated to dryness. No purification by precipitation/washing possible			Cake washed with water to remove impurities	
Step 2		Yield	8.31 g		Yield	70%
		Form	Brown oil		Form	Crystalline solid
		Famciclovir as a crude brown oil. Purity Approx. 30% by NMR.			Product of high purity (98%) and utilisable form for a pharmaceutical intermediate	
Step 3	Not Applicable				Yield	90%
					Form	Crystalline solid
					Famciclovir of pharmaceutical acceptable quality	
Overall Yield	0% (usable famciclovir) (weight yield 14%)			41% (usable famciclovir)		
Form	Crude Oil			Crystalline solid		